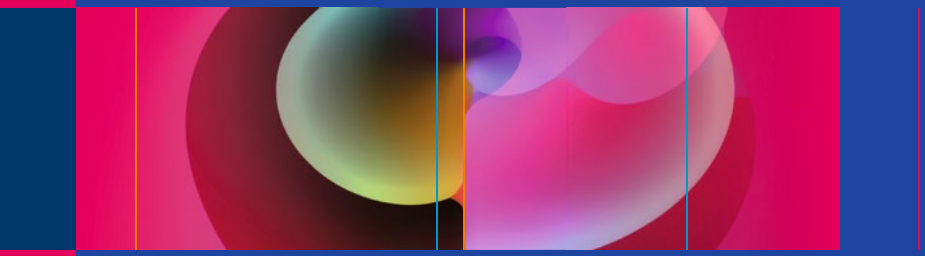
Heather L. Appelbaum
Editor



Abnormal Female Puberty

A Clinical Casebook

Springer

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Preface

Female pubertal development requires coordination of the hypothalamus, pituitary, and ovaries and an appropriate outflow tract to allow for menstrual egress. The balance that is essential for adequate pubertal progress is delicate, requiring the appropriate hormonal and metabolic milieu for development. The hormonal axis may be influenced by intrinsic factors or exogenous exposures which can disrupt the normal process, manifesting in early or delayed signs of reaching specific pubertal milestones. The goal of *Abnormal Female Puberty: A Clinical Casebook* is to provide the practicing gynecologist, endocrinologist, pediatrician, adolescent medicine specialist, or reproductive endocrinologist with a concise volume that illustrates the tools required to treat both simple and complex pubertal problems. It provides a framework for understanding how to evaluate, diagnose, and manage a myriad of female pubertal disorders.

Chapter topics were chosen to cover the most pertinent and prevalent areas of abnormal pubertal development that a practitioner may encounter. Each chapter is formatted such that the reader can identify a problem and gain additional understanding of the fundamentals that relate to the disorder as well as appropriate treatment strategies. The chapters are organized to include examples related to the structural, hormonal, genetic, and environmental effects on pubertal development. The chapters include clinical pearls to help reinforce key points and learning objectives. Chapter

authors were selected by the editor for their expertise in the field and asked to highlight real case examples to illustrate the focus of the respective chapters. The case book is a practical handbook that addresses various scenarios relating to abnormal pubertal development with the intention that the book can be used as a reference companion for further understanding focused clinical scenarios or used as an overview of abnormal female pubertal development.

I hope that this casebook becomes a frequently referenced guide for practicing physicians as well as allied health professionals, residents, fellows, or students who are interested in a greater appreciation of the factors that influence female pubertal development.

NY, USA Heather L. Appelbaum, MD

Contents

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Chapter 1
Congenital Anomalies and Abnormal Pubertal Development

Heather L. Appelbaum and Amy Vallerie

Abbreviations

17OHP	17-Hydroxyprogesterone
AIS	Androgen insensitivity
CAIS	Complete androgen insensitivity
DHEAS	DHEA-sulfate
DHT	Dihydrotestosterone
DSD	Disorders of sex development
FISH	Fluorescence in situ hybridization
FSH	Follicle-stimulating hormone
LH	Luteinizing hormone

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MDA	Müllerian duct anomaly
MRKH	Mayer–Rokitnsky–Küster–Hauser
PAIS	Partial androgen insensitivity
SRY	Sex determining region Y

Introduction

Primary amenorrhea in girls is a frequent cause for referrals to the endocrinologist or gynecologist. Structural abnormalities of the reproductive tract account for approximately 22 % of cases of primary amenorrhea [1]. History and physical examination typically confirm normal progression of pubertal milestones, including normal thelarche, pubarche, and growth in girls who have not menstruated. In examining the patients, particular attention should be paid to breast development and Tanner staging, the presence of axillary and pubic hair, and careful inspection of the external genitalia and hymenal orifice. Laboratory determinations should be done to confirm normal gonadotropin and sex steroid hormone levels. Karyotype with FISH determination of the SRY gene is useful to appreciate if there is discordance between the phenotype and genotype of the individual [2, 3]. Imaging studies are essential in all cases to augment the physical findings and clarify the internal reproductive structures. This chapter will provide a case-based approach to appreciate the complexities of primary amenorrhea as a result of congenital anomalies of the reproductive tract. Surgical and nonsurgical treatment modalities will be discussed.

Müllerian Agenesis

Case Presentation

A 16-year-old female is referred for primary amenorrhea. Breast development began at age 11 years and she has had axillary and pubic hair since age 12. Her general health is good. She was

diagnosed with scoliosis at age 9. She exercises regularly and eats a healthy, balanced diet. She is socially well adjusted. She is not sexually active and there is no family history of infertility.

On examination, her height 160 cm was and weight 59 kg; BMI was 21. Vital signs were normal. General habitus was normal for an adolescent girl. She had no acne or hirsutism. Pubertal status was Tanner stage 5 for breasts and pubic hair development and there was no clitoral enlargement. The hymen was annular and diminutive. Cotton-tipped applicator identified a 1 cm vaginal dimple. The urethra, perineum, and anus were normal.

Laboratory tests included normal thyroid functions, prolactin, luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, and DHEA-sulfate (DHEAS). Her early morning 17-hydroxyprogesterone (17OHP; tandem mass spectrometry assay) was normal and testosterone level was normal. Karyotype was 46, XX. Transabdominal pelvic ultrasound identified normal ovaries bilaterally, duplex kidneys bilaterally, and no uterus. MRI of the pelvis confirmed the duplex collecting system, normal ovaries bilaterally, and absence of Müllerian structures.

Discussion

The patient is 4 years past the onset of pubertal development. On average, menarche occurs 2 years following thelarche and correlates with a Tanner stage 3–4 breast development. Patients should be referred for evaluation of abnormal puberty (1) at age 13 if thelarche has not yet occurred, (2) 3 years post thelarche in the absence of menstruation, and (3) at age 15 years if menarche has not yet occurred in the setting of normal secondary sexual development.

In this case, the history and clinical examination demonstrate normal development of secondary sexual characteristics in the absence of a vagina, consistent with Müllerian agenesis. Pelvic ultrasound is an accurate, inexpensive, and often readily available modality to confirm the rudimentary development of the uterus.

Her 46, XX genotype eliminates the possibility of complete androgen insensitivity syndrome (CAIS), a disorder of sex development that must be considered in the differential diagnosis of vaginal agenesis [2]; see Case 3 for further discussion.

Mayer–Rokitansky–Küster–Hauser (MRKH), or congenital absence of the uterus and vagina, is prevalent in the general population affecting 1 in 4500 live female births [4]. Patients have normal ovarian tissue and function, resulting in seemingly normal pubertal development until they fail to menstruate. The paramesonephros fails to develop appropriately, leading to variable rudimentary Müllerian structures. In approximately 5 % of patients, a functional endometrium will be found within an underdeveloped uterine structure. MRKH is currently thought to result from multiple autosomal genetic and chromosomal defects [5].

MRKH must be distinguished from CAIS in which the androgen receptor is unable to recognize androgen hormones with resultant persistence of rudimentary Wollfian duct system, undescended testicular gonads, and failure to develop secondary male sexual characteristics and an absent Müllerian system. Although treatment recommendations for creating a neovagina are the same, pathogenesis and reproductive capacity are significantly different. Patients with MRKH can be reassured that ovarian tissue and function is normal and, therefore, timing and duration of hormonal changes are expected to be similar to that of the general population.

Pelvic imaging highlights the association of Müllerian anomalies with renal anomalies. Simultaneous embryologic development of the paramesonephros (Müllerian system) and metanephros (renal system) yields a 30–50 % association rate of Müllerian duct anomalies (MDA) with renal anomalies [4, 6, 7]. Vertebral and nonvertebral skeletal abnormalities are noted in approximately 7–14 % and 29–44 % of patients, respectively. Cardiac defects (16 %) and ear anomalies with and without hearing loss (up to 25 %) have been reported in several studies [8–10]. The association of cervicothoracic somite dysplasia with MDA and renal anomalies is referred to as MURCS [11].

Management

The first line treatment for creating a neovagina for girls with MRKH is vaginal self-dilation [12, 13]. The timing should be individualized to reflect the psychosocial and psychosexual maturity of the individual. Success with vaginal dilation may be improved when readiness is properly assessed prior to initiating the self-dilation process [13]. Patients who are unable to tolerate self-dilation may be a candidate for minimally invasive surgical techniques that allow for mechanical dilation, such as the modified Vecchietti or Davydov procedure [14–16]. Alternatively, graft vaginoplasty which employs skin, bowel, buccal mucosa, peritoneum, or other artificial means to create a neovagina can be used [17–20]. Concomitant psychosocial intervention may help self-image and improve sexual outcomes [21].

Patients should be reassured that there are multiple methods of creating a family. Adoption is a well-established and available process. Fertility is possible via gestational surrogacy, but may be limited by cost, cultural and ethical issues, and legal concerns. Research in the field of uterine transplant is currently in the development and exploration stages. To date, 11 uterine transplants have been performed, 7 successfully, with 1 reported live preterm birth. Further investigation will yield information regarding candidacy, safety, ethics, and reproductive outcomes [22–24].

This patient was counseled on surgical and nonsurgical options to create a neovagina by a gynecologist with experience in treating girls with vaginal agenesis. She was evaluated by a social worker with expertise in reproductive congenital anomalies for readiness using standardized and nonstandardized methods for assessing mental health; body image; commitment to treatment; and sexual maturity level including comprehension, awareness, and desire. Additionally, the logistics for privacy and personal motivation for treatment were addressed. Vaginal dilation using serial Syracuse dilators was initiated under the guidance of the gynecologist. Self-dilation instructions were provided and the method was demonstrated in the office. The patient privately employed this method for

20 minutes daily. Short-term follow-up confirmed accurate and effective technique. Interval multidisciplinary assessment of physical and psychological well-being confirmed normal neovaginal mucosa and surrounding urogenital structures and appropriate psychosocial adjustment. Fertility options were discussed but ultimately deferred.

Outcome

The patient created an 8 cm neovagina after dilating daily for 4 months. She is sexually active with a male partner. There is no dyspareunia and she reports unlimited sexual satisfaction for both herself and her partner. She has discontinued regular usage of the dilator and has been instructed to resume dilation twice weekly to maintain the neovagina in the absence of regular intercourse.

Clinical Pearls/Pitfalls

1. Vaginal agenesis should be considered in girls with amenorrhea and normal pubertal progression.
2. Müllerian agenesis is diagnosed by physical examination and confirmed with pelvic imaging.
3. Karyotyping is necessary to rule out androgen insensitivity syndromes.
4. Müllerian agenesis may be associated with renal anomalies or other congenital malformations including auditory, skeletal, cardiac, and anorectal malformations.
5. Timing and method for creating a neovagina should be individualized and based on the patient's maturity level and personal motivation. Success with self-dilation is improved with a multidisciplinary approach.
6. Girls with Müllerian agenesis are fertile despite not being unable to carry a pregnancy. Further investigation in the field of uterine transplant is warranted.

Imperforate Hymen

Case Presentation

A 12-year-old girl is referred for amenorrhea and cyclic pelvic pain for the last six months. Breast development began at age 10 years. Additional history included recent development of urinary retention and constipation. Physical examination was notable for Tanner stage 4 breasts and pubic hair development. There was no hirsutism or acne. Height was 156 cm and weight was 49 kg. The abdomen was soft, but there was a tender palpable mass above the pubic bone. There was no rebound or guarding. Examination of the external genitalia identified an imperforate hymen without any genital ambiguity. The hymen protruded with Valsalva maneuvering and with applying pressure to the suprapubic mass (Fig. 1.1a). The urethra and anus were normal.

Laboratory tests showed normal post pubertal levels of gonadotropins and normal levels of estradiol and testosterone. Transabdominal pelvic ultrasound identified a large hematometrocolpos and normal ovaries bilaterally (Fig. 1.1b).

Discussion

This patient has the classic presenting symptoms of an obstructive reproductive anomaly including normal secondary sexual characteristics, cyclic abdominal/pelvic pain, and secondary pressure symptoms. Imperforate hymen, the most common obstructive anomaly of the reproductive tract, occurs in 1 in 1000–2000 girls [25, 26]. Following several menstrual cycles, the vagina distends and cyclic pain worsens as menstrual fluid accumulates within the vaginal canal. Imperforate hymen is diagnosed on physical exam with visualization of a hymenal bulge. Pelvic imaging confirms obstruction to menstrual egress by identifying hematocolpos (see Fig. 1.1b). The differential diagnosis for amenorrhea associated with hematocolpos includes imperforate

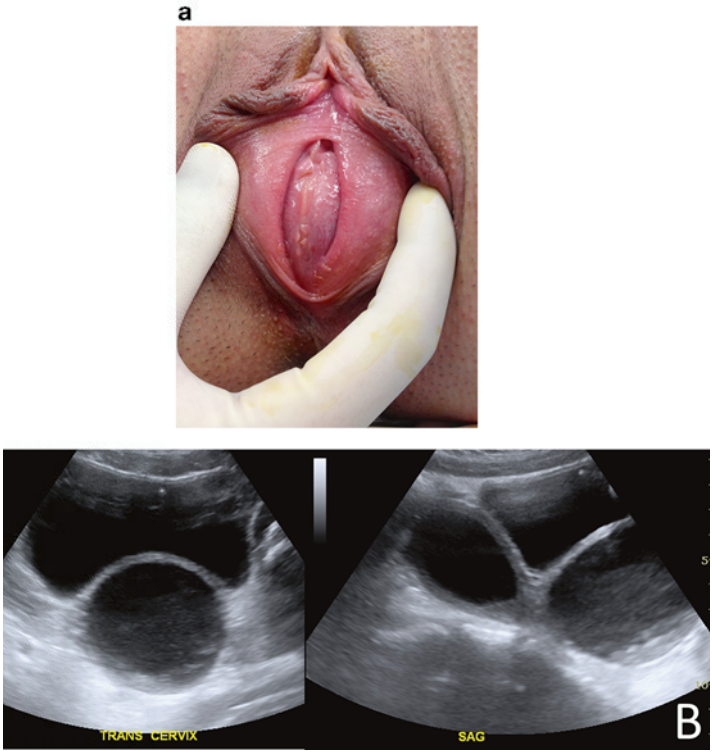

Fig. 1.1 (**a**) Imperforate hymen, (**b**) transabdominal pelvic ultrasound illustrating hematometracolpos

hymen, transverse vaginal septum, segmental vaginal agenesis, and cervical dysgenesis. Patients most often present in early adolescence; however, prenatal and neonatal diagnosis can be made when an abdominal or perineal mass consistent with a mucocolpos is noted on ultrasound or clinical examination. In neonates, a mucocolpos may be associated with other congenital anomalies, such as a cloaca malformation or persistent urogenital sinus. In

the case of an isolated hymenal anomaly, surgical treatment is typically delayed until puberty unless compressive symptoms such as urinary retention, hydronephrosis, or respiratory distress develop [27, 28]. Surgical management in a symptomatic neonate should be approached by an experienced multidisciplinary surgical team in order to avoid misdiagnosis, unnecessary procedures, and potential complications [29].

The absence of a bulge upon Valsalva maneuvering or the presence of a shortened vagina without palpable cervix is concerning for a complex Müllerian duct anomaly (MDA). Pelvic MRI is needed to assess the degree and exact location of the defect within the vaginal canal to allow for adequate surgical planning [30, 31]. Transverse vaginal septum is distinguished from segmental vaginal agenesis by a thickness less than 1 cm [32]. A transverse vaginal septum can be excised and the vaginal mucosa reapproximatd with a "Z" plasty technique; however, Segmental vaginal agenesis may require preoperative dilation to reduce the distance between the upper and lower vagina or use of a graft to bridge or lengthen the vaginal canal [28]. Needle aspiration or drainage of hematocolpos should not be attempted as this can introduce bacteria into a closed and sterile environment and may lead to severe pelvic inflammatory disease or sepsis. Complications, such as endometriosis, pelvic abscess, chronic pelvic pain, or infertility associated with outflow tract obstructions can be prevented with surgical intervention to restore the conduit for menstrual egress. Referral should be made to a surgeon with specific expertise in congenital anomalies of the reproductive tract [28, 33]. Hormonal suppressive therapy should be provided if treatment delay is necessary and foley catheter insertion may be indicated to ameliorate urinary retention [34]. Laparoscopic or percutaneous drainage of the hematocolpos is a potential sterile technique which can relieve patient discomfort in patients who fail hormonal suppressive therapy and require treatment delay [35].

Management

A hymenotomy is the appropriate treatment for imperforate hymen. Foley catheter was inserted to empty the bladder and a cruciate hymenal incision allowed for decompression of the large hematocolpos with expression of copious thick brown blood (see Fig. 1.2a, b). Circumferential interrupted sutures placed to reapproximate the vaginal mucosa to the hymenal periphery was performed by a gynecologist experienced in the field of congenital reproductive anomalies (see Fig. 1.2c).

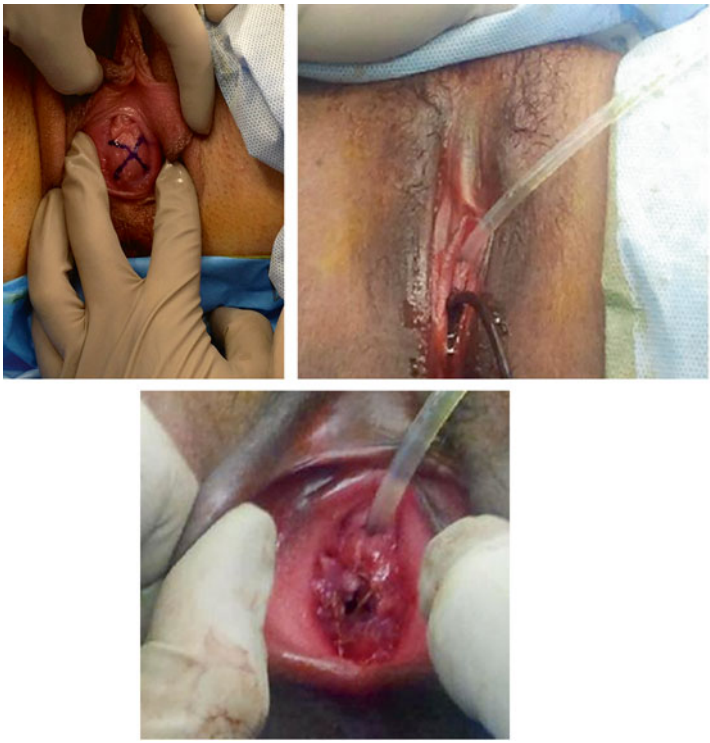

Fig. 1.2 (**a**) demarcation of the hymenal tissue outlines the cruciate incision in the hymenal tissue, (**b**) evacuation of hematocolpos, and (**c**) circumfrential interrupted sutures reapproximate the hymenal periphery to the vaginal mucosa

Outcomes

The pelvic pain resolved and the patient has regular menstrual periods. She is able to use tampons without difficulty. Postoperative dilation of the hymenal orifice is not necessary and no functional or reproductive deficits are anticipated [36].

Clinical Pearls/Pitfalls

1. Girls with normal pubertal progression, amenorrhea, and cyclic pelvic pain should be evaluated for reproductive outflow tract obstruction.
2. Imperforate hymen can be diagnosed in infancy with proper and thorough genital examination.
3. Ideal timing for hymenotomy is during early puberty, prior to menarche. Early diagnosis allows for early intervention and prevents short-term and long-term morbidity associated with outflow tract obstructions.
4. With proper surgical technique, no long-term functional or reproductive deficits are anticipated and postoperative dilation of the hymenal orifice should not be necessary

Androgen Insensitivity

Case Presentation

A 17-year-old girl is referred for primary amenorrhea. Breast and pubic hair development began at age 11 years. She is in general good health. There are no urinary complaints. She does not take any medications, vitamins, or supplements. She does not exercise regularly and she eats a healthy, balanced diet. She is not sexually active. She has no social complaints. There is a family history that

is significant for two maternal aunts and a maternal cousin who did not have children.

On examination, her height is 167 cm and weight is 56 kg. Vital signs are normal. She does not have acne or hirsutism. She has sparse pubic and axillary hair and breast development is consistent with Tanner stage 5. There is a palpable mass in the left labia and in the right inguinal canal. The clitoris measures 3.5×1.2 cm on maximum stretch. The labia are normal and do not appear rugated, pigmented, or fused. There is a 2.0 cm vaginal dimple. The urethra and anus are normal.

Laboratory tests included karyotype 46, XY with positive SRY gene. Total testosterone level is 170 ng/dL, dihydrotestosterone (DHT) is 27 g/dL. Ultrasound identified absence of uterus and ovaries and confirmed right inguinal and left labial testes.

Discussion

Excess androgen hormone production in adolescent females can result in menstrual abnormalities, hirsutism, excess acne, clitormegaly, male pattern baldness, deepening of the voice and increased muscle bulk in a male distribution. The differential diagnosis associated with signs of virilization includes androgen secreting tumors, exogenous androgen exposure, late onset congenital adrenal hyperplasia, polycystic ovarian syndrome, and disorders of sexual development (DSD).

DSDs occur when the genotype of the individual is discordant with the phenotypic expression of the internal reproductive organs and/or the external genitalia of the individual [57]. 46, XX karyotype associated with late onset congenital adrenal hyperplasia is more likely to present with changes in menstrual cycle rather than primary amenorrhea. A 46, XY genotype may present with phenotypic variability ranging from genital ambiguity to normal appearing female genitalia. The DSDs associated with primary amenorrhea, genital ambiguity, and 46, XY karyotype include

defects of androgen receptor function, disorders of androgen synthesis, 5 alpha reductase deficiency, and ovotesticular DSD [2, 37]. Androgen receptor impairment is differentiated from defects in testosterone synthesis or 5-alpha reductase deficiency by assessing the serum levels of testosterone and dihydrotestosterone (DHT). Androgen receptor defects can be differentiated from 5 alpha reductase deficiency because DHT production is normal in patients with androgen receptor defects and therefore the ratio of testosterone to DHT is normal.

Androgen insensitivity (AIS) is caused by a qualitative mutation in the X chromosome androgen receptor gene which makes an individual with genetic male potential resistant to the virilizing effect of testosterone and DHT. The prevalence of androgen receptor disorders is rare and approximates 1/20,000 genetic male live births [38]. These disorders are inherited as X-linked recessive and specific mutations of the receptor have been identified in families with AIS. The diagnosis of androgen receptor defect can be made by genetic sequencing. Partial androgen insensitivity (PAIS) may be due to amino acid substitutions in the hormone-binding domain of the receptor resulting in relative hormone resistance [39].

Varying degrees of androgen receptor impairment results in a relative resistance to the action of androgens. Individuals with complete androgen insensitivity (CAIS) have severe impairment of the androgen receptor function and present as normal phenotypic females with primary amenorrhea and absence of vagina and Müllerian structures (short blind ended vaginal pouch or absent vagina) with normal male testosterone levels. The Wolffian system and prostate are also absent. While both have normal breast development, these patients can be differentiated clinically from those with MRKH by the absence of axillary and pubic hair. In most cases of AIS, testes are located in the abdomen, inguinal region, or in the labia majora and testosterone levels are in the normal male range [40]. Women with PAIS have less impairment of the androgen receptor. As a result, the presenting phenotype is highly variable and the patient may present anywhere along the spectrum of a mildly virilized female to an undervirilized male with gynecomastia [39, 41]. These patients may have genital ambiguity in the

setting of normal breast development and female body habitus. Pubic and axillary hair distribution varies from sparse to normal. The internal male reproductive structures may be partially or fully developed.

Optimal clinical management of individuals with DSD should include evaluation and long-term management performed at a center with an experienced multidisciplinary team including subspecialists in endocrinology, surgery, urology, gynecology, psychology, psychiatry, and genetics who are able to provide neonatal, pediatric, and adolescent care as well as transitional care into adulthood [2, 37]. Consideration should be given to the external genital appearance, genetics, internal reproductive structures, hormonal milieu, future fertility potential, and additional ethical, psychosocial, and familial issues in order to determine the gender assignment in a presenting newborn. Management for PAIS in phenotypic females is directed at preventing further manifestations of virilization at the time of puberty. Testosterone levels will decrease in response to gonadectomy. Bilateral gonadectomy is recommended to prevent malignant degeneration of cryptorchid testes. Malignancy risk varies with the DSD, location of the gonad, and patient age. Germ cell tumors and gonadoblastoma occur in about 1–4 % on undescended testes [42]. Intratubular germ cell neoplasia, a noninvasive precursor lesion has been reported in 6 % and 15 % of pediatric patients with CAIS and PAIS, respectively [43]. The lifetime risk of malignancy in patients with PAIS may be as high as 50 % and therefore gonadectomy is recommended at the time of diagnosis [37, 44, 45]. In girls with CAIS, malignancy risk is 3.6 % before age 25 years. Therefore, gonadectomy can be delayed until sexual maturation is complete so that normal pubertal growth spurt and development of secondary sexual characteristic can occur. Gonadectomy is recommended following completion of puberty as cumulative malignancy risk increases and surpasses 30 % by age 50 years [44, 46].

Gonadectomy renders the individual infertile and estrogen hormone replacement therapy is recommended to preserve bone health, minimize vasomotor symptoms, and to maintain an overall

sense of well-being [33, 47, 48]. Cosmetic surgery including clitoroplasty and vaginoplasty should be determined on an individual basis and sometimes can be avoided. When surgery is indicated, emphasis should be placed on functional outcome rather than strictly on cosmetic appearance with the goal of preserving erectile function and innervation of the clitoris [2, 37]. Nonsurgical and surgical techniques for creating a neovagina are discussed above and should be deferred until the patient approaches sexual maturity. Psychological counseling for the patient and caregivers can be beneficial to appropriately guide the child as she approaches different psychosocial milestones [47–49]. The data regarding psychologic outcomes in patients with DSD is often reported as a collective group rather than a single diagnosis given the rarity of these conditions and further studies are needed to clarify disease-specific psychological implications. Despite a lack of data specific to AIS, expert opinion and cumulative data support the assistance of a therapist experienced with DSD to help guide the patient and family through cognitively appropriate disclosure of the diagnosis and to aid with gender identity [48]. This is a critical component of patient care, as DSD patients have been shown to have high rates of suicidal thoughts and anxiety compared to controls [50]. Teens with DSD have fewer close friendships and love experiences compared to their peers, and as adults 46XY women demonstrate lower femininity scores [51]. In a study of patients with XY DSD, patients reported higher fear of sexual contact, decreased sexual desire, increased issues with arousal, increased sexual pain, and higher rates of dissatisfaction with their overall sex life compared to controls [52].

Androgen insensitivity syndromes are generally considered incompatible with fertility. Due to the SRY gene, the Müllerian structures regress. In patients with CAIS, the Wolffiann system is also underdeveloped. Changes in gonadal histology, including loss of germ cells and tubular atrophy take place in early childhood [43]. While successful uterine transplantation and pregnancy following IVF have recently been reported, all patients had a 46XX karyotype and uterine infertility due to agenesis or hysterectomy

[22, 23]. The role of uterine transplantation in patients with DSD has not yet been explored, but a review of patients who applied for the uterine transplant project at Akdeniz University Hospital demonstrated that 8.4 % of applicants had CAIS [53]. The feasibility of uterine transplant in DSD patients is unknown given differences in anatomy, requirements for donor oocytes and hormonal support and ethical consideration.

Patients with PAIS have variable development of the Wolffian system and prostate. Literature review demonstrates case reports of male patients with mild PAIS who have been able to preserve fertility. Clinically, these patients present as undervirilized males with gynecomastia and have low ejaculation and/or semen volumes [39] or conceive spontaneously [54]. Assisted reproductive technologies, such as testicular extraction of sperm with intracytoplasmic sperm injection may be necessary to overcome these obstacles [55, 56].

Optimal care of the individual with a DSD requires the attention from a multidisciplinary team of specialists. Ideally, a comprehensive team is comprised of specialists in the fields of endocrinology, urology, gynecology, genetics, and mental health professionals who appreciate the unique issues pertaining to caring for these individuals, including issues related to sex assignment, gender identity, sexual orientation, sexual functioning, pubertal development, fertility potential, body image, and overall psychosocial well-being of the patients and their caregivers.

Management

In this case, psychosocial assessment confirmed a female sexual identity and an adequate understanding of her diagnosis. The patient underwent a bilateral gonadectomy and a nerve sparing clitoroplasty. She was started on an estradiol patch for hormone replacement therapy to preserve bone health and overall sense of well-being. Progesterone was not indicated due to the lack of Müllerian structures and menses was not anticipated. Postoperatively, she was instructed to apply moderate pressure to

the vaginal mucosa with a dilator for 20 min each day in order to create a neovagina using native mucosa and serial dilations. Psychosocial assessment and intervention with a social worker who is knowledgeable about the issues pertaining to individuals with DSDs was maintained throughout her care.

Outcomes

She is tolerating the hormone replacement therapy well. She is psychosocially well adjusted. There are no urinary complaints and clitoral sensation is uncompromised. A neovagina was successfully created with progressive perineal self-dilation. She is sexually active with one male partner without difficulty. Usage of the dilator has been discontinued. She continues to follow up with the multidisciplinary group of physicians and a social worker who specializes caring for patients with DSD.

Clinical Pearls and Pitfalls

1. Karyotyping and genetic testing are useful tools in evaluating patients with primary amenorrhea and genital ambiguity.
2. DSDs occur when the genotype and the phenotype of an individual are discordant.
3. Individuals with DSD and a female sex assignment often experience primary amenorrhea.
4. Gonadectomy is recommended for patients with androgen insensitivity syndromes to prevent malignant transformation of the testes and to prevent virilization effects for patients with incomplete androgen receptor defects who have a female sexual identity. Gonadectomy is recommended at the time of diagnosis in patients with PAIS, but can be delayed until puberty is complete in patients with CAIS.
5. Hormone replacement therapy is necessary following gonadectomy.